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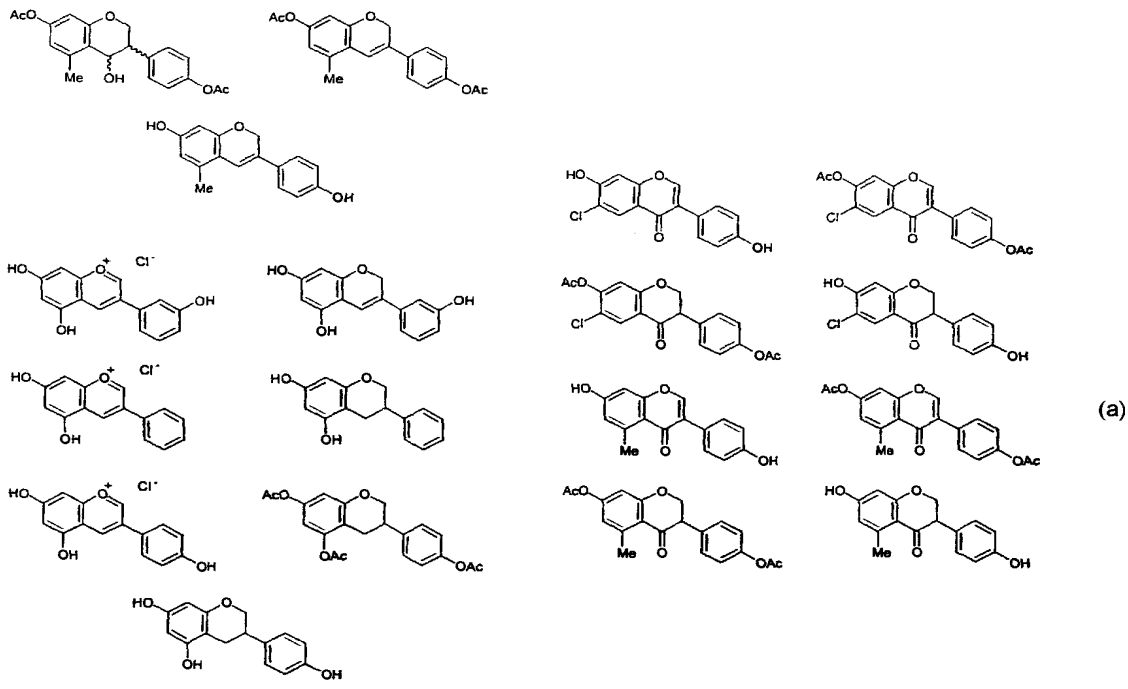
(54) Title: COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF



(a)

(57) Abstract: Isoflavone compounds are described and recommended as therapeutic agents. Exemplified and preferred compounds are (a). Indications show compounds have good competitive binding to estrogen receptors. This is exemplified.

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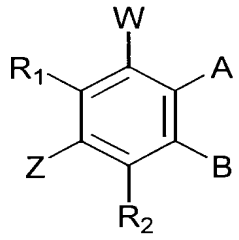
COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF

This invention relates to compounds, formulations, drinks, foodstuffs, methods and therapeutic uses involving, containing, comprising, including and/or for preparing certain isoflavone compounds and analogues thereof.

According to an aspect of this invention there is provided isoflavone compounds and analogues thereof of the general formula I:



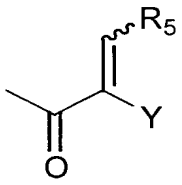
(I)

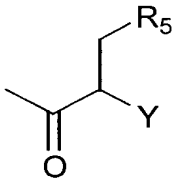
in which

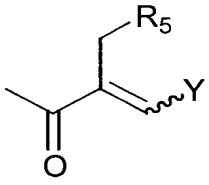
R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z is hydrogen, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

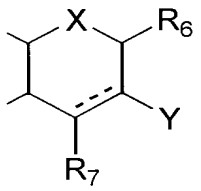
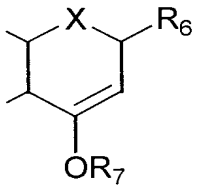
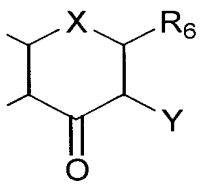
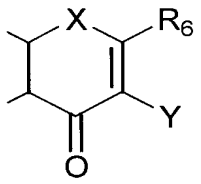
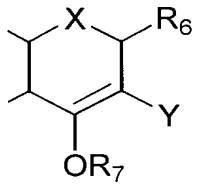




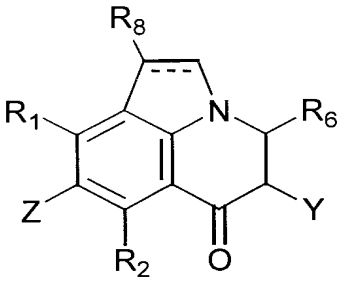
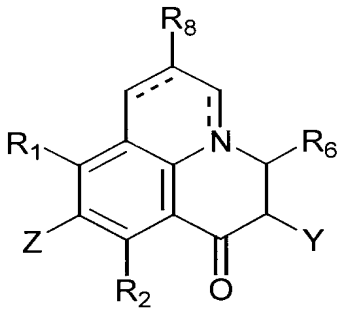
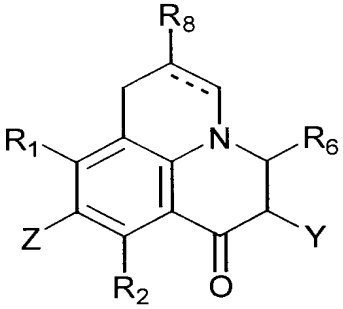


, or

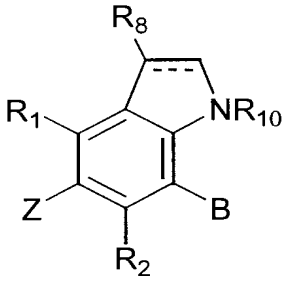
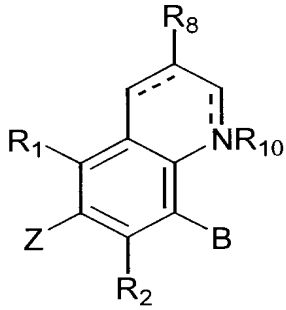
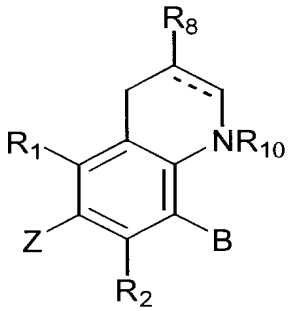
W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from






, or

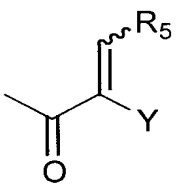
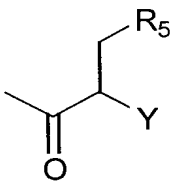
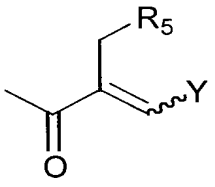
W, A and B taken together with the groups to which they are associated comprise




, or

W and A taken together with the groups to which they are associated comprise

and B is

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

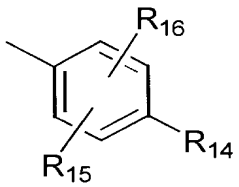
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

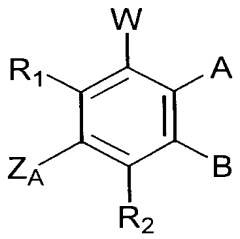
R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_1 is not hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid.

According to another aspect of this invention there is provided isoflavone compounds and analogues thereof of the general formula II:



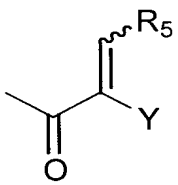
(II)

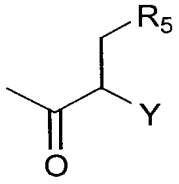
in which

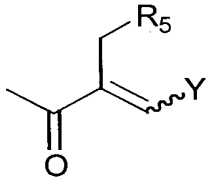
R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z_A is OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

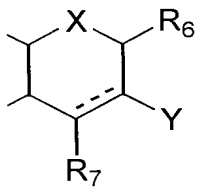


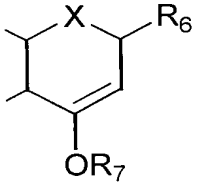


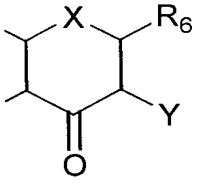


, or

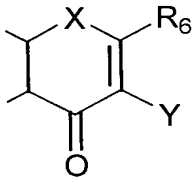
W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from

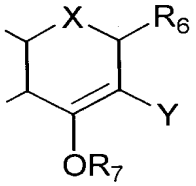




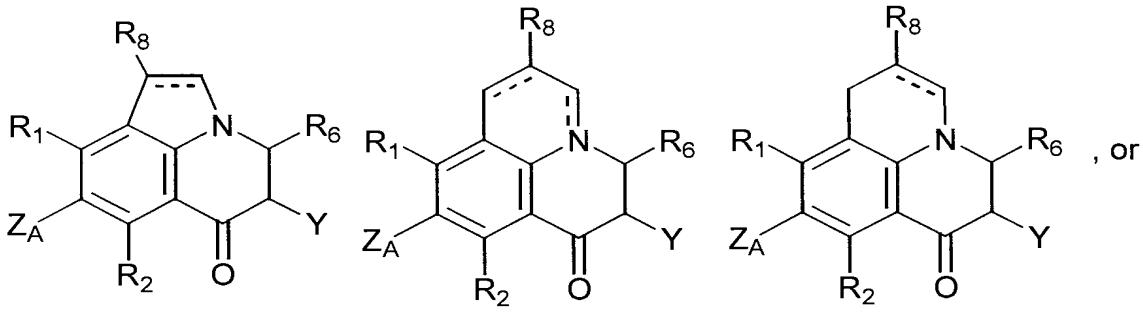


, or



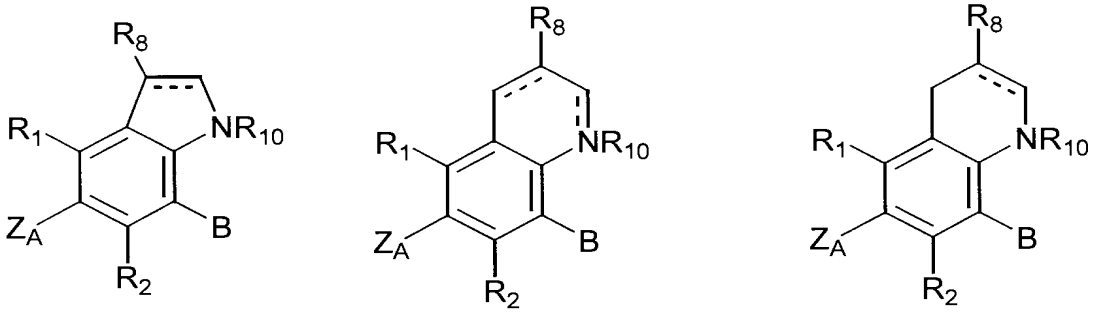


W, A and B taken together with the groups to which they are associated comprise

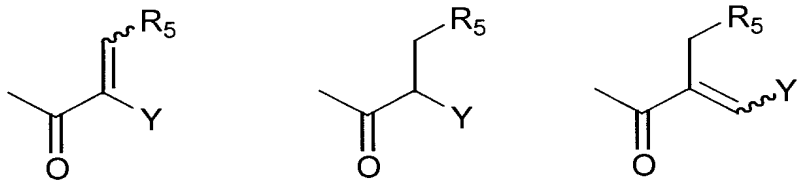


, or

W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

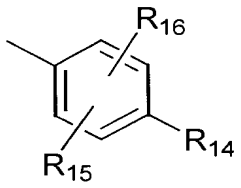
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

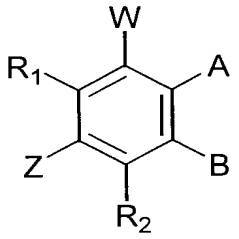
Y is



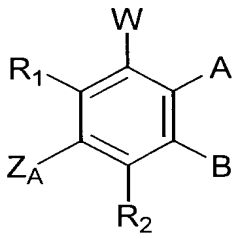
wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo.

It has surprisingly been found by the inventors that compounds of the general formulae I and II:



(I)



(II)

in which

R_1, R_2, W, A, B, Z and Z_A are as defined above have particular utility and effectiveness in the treatment, prophylaxis, amelioration defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; atherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts.

Thus according to another aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; artherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern

baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds of formulae I and II as defined above.

Yet another aspect of the present invention is the use of compounds of formulae I and II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

Still another aspect of the present invention is the use of one or more compounds of formulae I and II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

And another aspect of the present invention comprises an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises one or more compounds of formulae I and II either alone or in association with one or more carriers or excipients.

A further aspect of the invention is a therapeutic composition which comprises one or more compounds of formulae I and II in association with one or more pharmaceutical carriers and/or excipients.

A still further aspect of the present invention is a drink or food-stuff, which contains one or more compounds of formulae I and II.

Another aspect of the present invention is a microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds of formulae I and II.

Still another aspect of the present invention relates to one or more microorganisms which produce one or more compounds of formulae I and II. Preferably the microorganism is a purified culture, which may be admixed and/or administered with one or more other cultures which product compounds of formulae I and II.

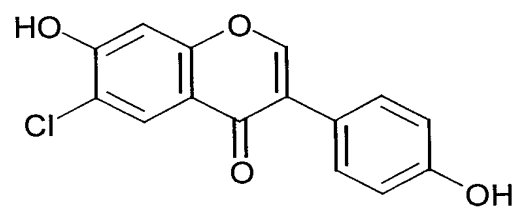
Throughout this specification and the claims which follow, unless the text requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like. The alkyl group has 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably methyl, ethyl propyl or isopropyl. The alkyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino-carbonyl, di-(C_1-C_4-alkyl)-amino-carbonyl, hydroxyl, C_1-C_4-alkoxy, formyloxy, C_1-C_4-alkyl-carbonyloxy, C_1-C_4-alkylthio, C_3-C_6-cycloalkyl or phenyl.

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, carbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylcarbonyloxy or halo.

The term "halo" is taken to include fluoro, chloro, bromo and iodo, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" will include monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred haloalkyl groups are trifluoromethyl and pentafluoroethyl.

Particularly preferred compounds of the present invention are selected from: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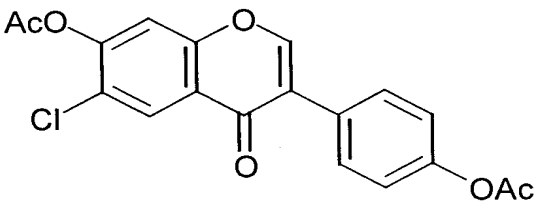
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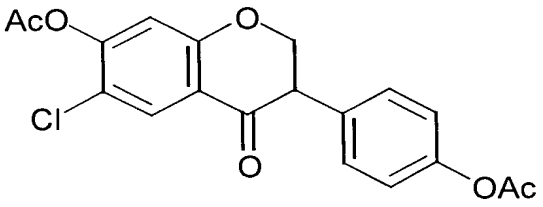
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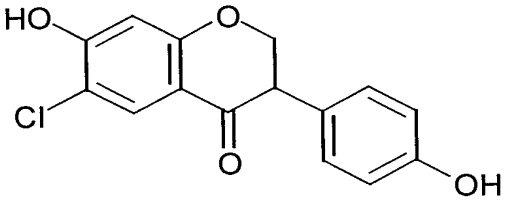
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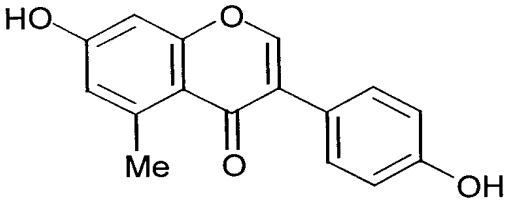
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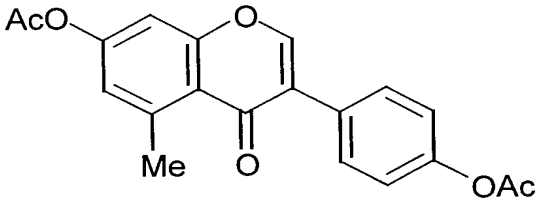
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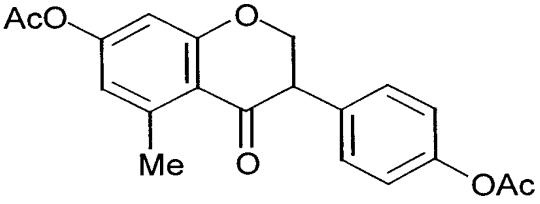
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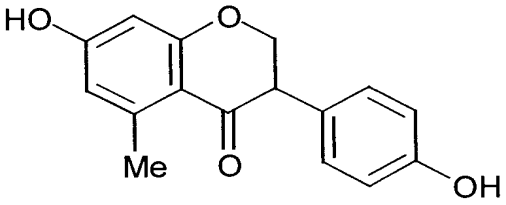
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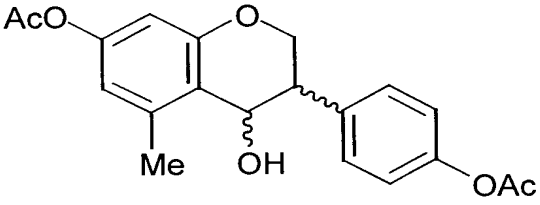
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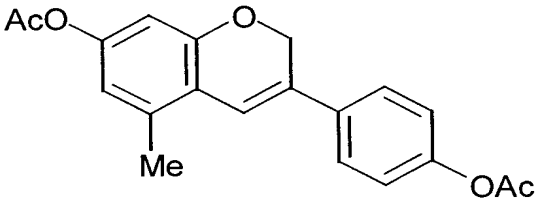
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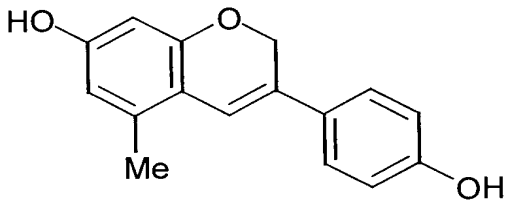
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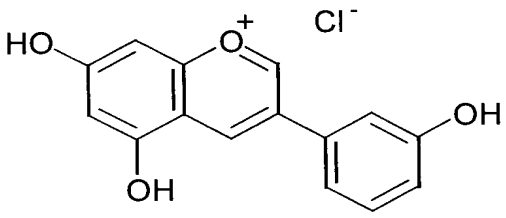
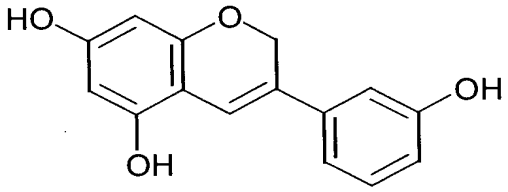
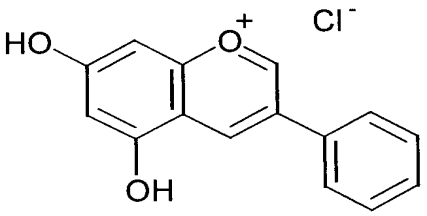
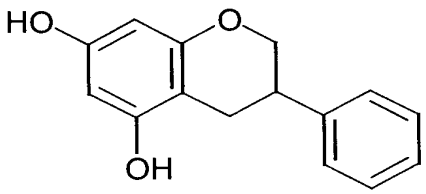
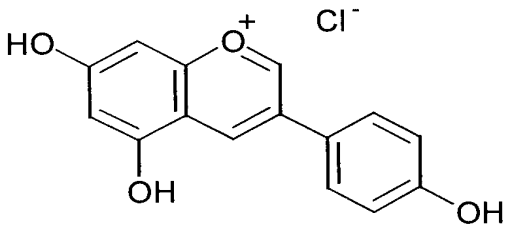
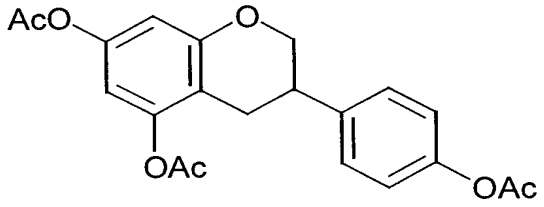


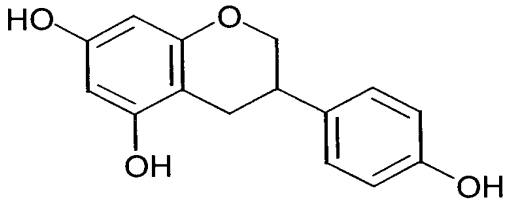












Compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic effects, vasodilatory and spasmodic effects, inflammatory effects and oxidative effects.

The amount of one or more compounds of formulae I and II which is required in a therapeutic treatment according to the invention will depend upon a number of factors, which include the specific application, the nature of the particular compound used, the condition being treated, the mode of administration and the condition of the patient. Compounds of formulae I or II may be administered in a manner and amount as is conventionally practised. See, for example, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1299 (7th Edition, 1985). The specific dosage utilised will depend upon the condition being treated, the state of the subject, the route of administration and other well known factors as indicated above. In general, a daily dose per patient may be in the range of 0.1 mg to 2 g; typically from 0.5 mg to 1 g; preferably from 50 mg to 200 mg.

The production of pharmaceutical compositions for the treatment of the therapeutic indications herein described are typically prepared by admixture of the compounds of the invention (for convenience hereafter referred to as the "active compounds") with one or more pharmaceutically or veterinarially acceptable carriers and/or excipients as are well known in the art.

The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the subject. The carrier or excipient may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose, for example, a tablet, which may contain from 0.5% to 59% by weight of the active compound, or up to 100% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, optical, buccal (for example, sublingual), parenteral (for example, subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any

given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulation suitable for oral administration may be presented in discrete units, such as capsules, sachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture such as to form a unit dosage. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of the free-flowing, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sublingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compounds, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may

conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1% to 60% w/v of active compound and are administered at a rate of 0.1 ml/minute/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations or compositions suitable for topical administration to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combination of two or more thereof. The active compound is generally present at a concentration of from 0.1% to 0.5% w/w, for example, from 0.5% to 2% w/w. Examples of such compositions include cosmetic skin creams.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 M to 0.2 M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research 3* (6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 M to 0.2 M active ingredient.

The active compounds may be provided in the form of food stuffs, such as being added to, admixed into, coated, combined or otherwise added to a food stuff. The term food stuff is used in its widest possible sense and includes liquid formulations such as drinks including dairy products and other foods, such as health bars, desserts, etc. Food formulations containing compounds of the invention can be readily prepared according to standard practices.

Compounds of the present invention have potent antioxidant activity and thus find wide application in pharmaceutical and veterinary uses, in cosmetics such as skin creams to prevent skin ageing, in sun screens, in foods, health drinks, shampoos, and the like.

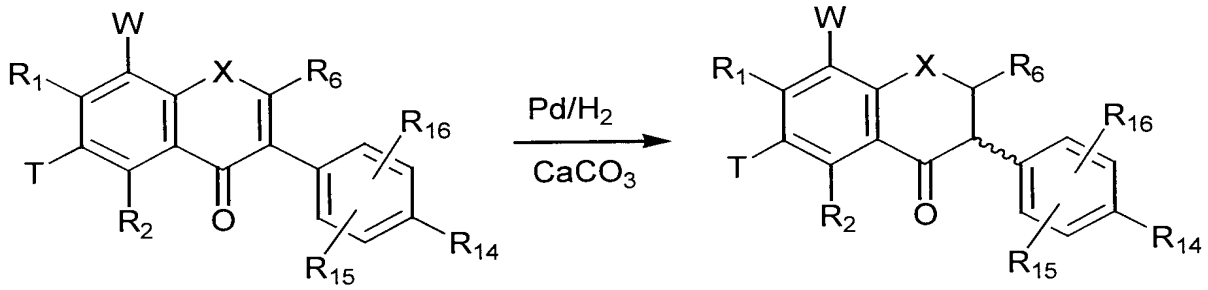
It has surprisingly been found that compounds of the formulae I or II interact synergistically with vitamin E to protect lipids, proteins and other biological molecules from oxidation.

Accordingly a further aspect of this invention provides a composition comprising one or more compounds of formulae I or II, vitamin E, and optionally a pharmaceutically, veterinarially or cosmetically acceptable carriers and/or excipients.

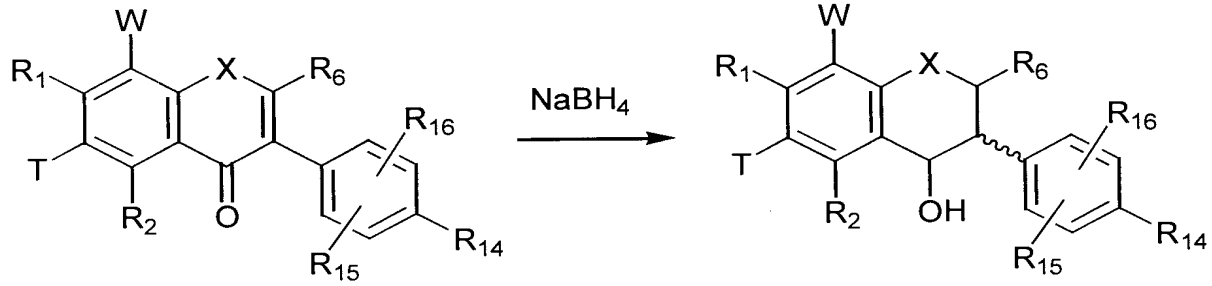
Therapeutic methods, uses and compositions may be for administration to humans or animals, such as companion and domestic animals (such as dogs and cats), birds (such as chickens, turkeys, ducks), livestock animals (such as cattle, sheep, pigs and goats) and the like.

Compounds of formulae I and II may be prepared by standard methods known to those skilled in the art. Suitable methods may be found in, for example, International Patent Application WO 98/08503 which is incorporated herein in its entirety by reference. Methods which may be employed by those skilled in the art of chemical synthesis for constructing the general ring structures depicted in formulae I and II are depicted in schemes 1-8 below. Chemical functional group protection, deprotection, synthons and

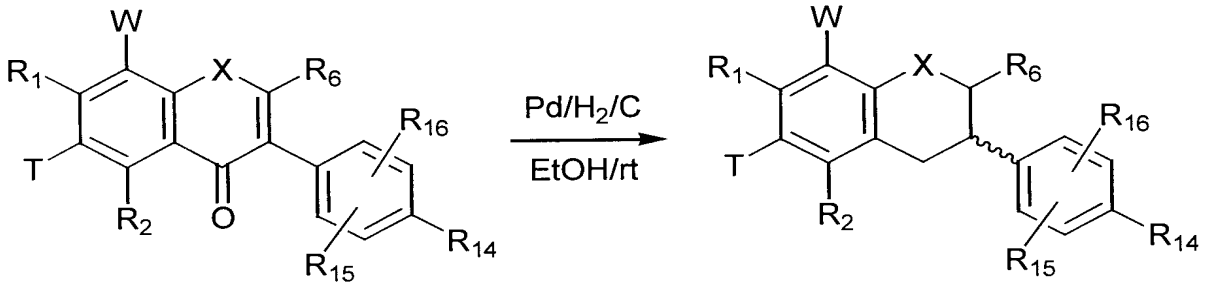
other techniques known to those skilled in the art may be used where appropriate in the synthesis of the compounds of the present invention. In the formulae depicted in the schemes below the moities R_1, R_2, R_6, R_8, R_{14}, R_{15}, R_{16}, W and X are as defined above. The moiety T is either Z or Z_A as defined in formulae I or II above. Reduction of the isoflavone derivatives may be effected by procedures well known to those skilled in the art including sodium borohydride reduction, and hydration over metal catalysts such as Pd/C, $Pd/CaCO_3$ and Platinum(IV)oxide (Adam's catalyst) in protic or aprotic solvents. The end products and isomeric ratios can be varied depending on the catalyst/solvent system chosen. The schemes depicted below are not to be considered limiting on the scope of the invention described herein.



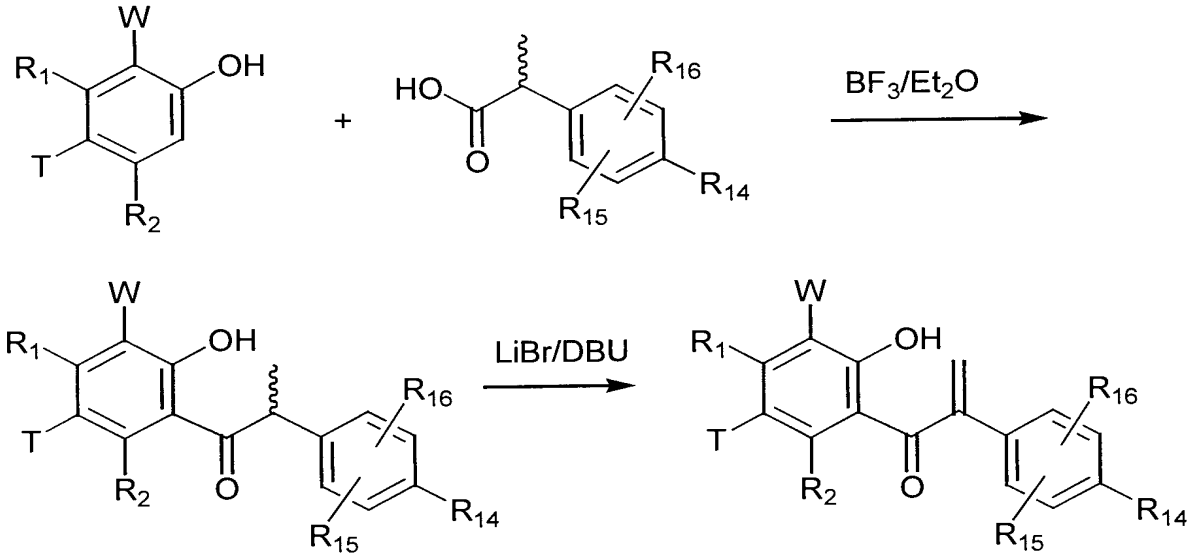
Scheme 1



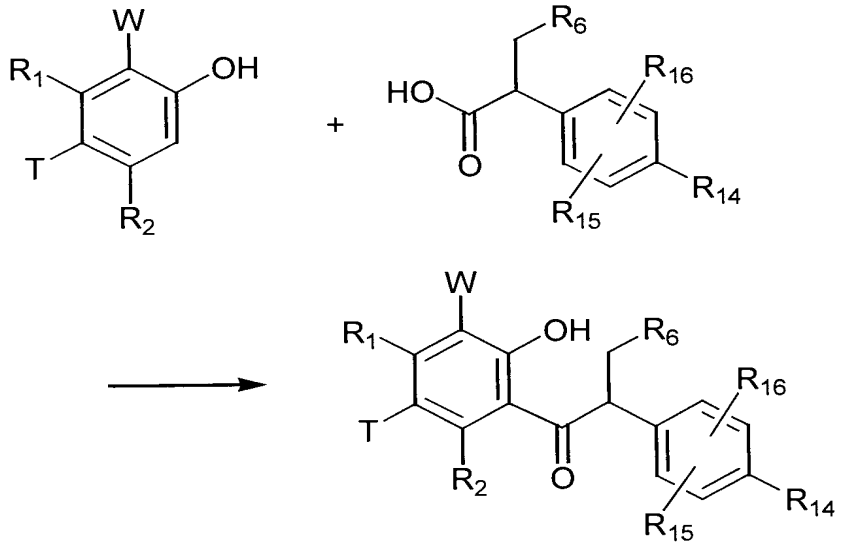
Scheme 2



Scheme 3



Scheme 4



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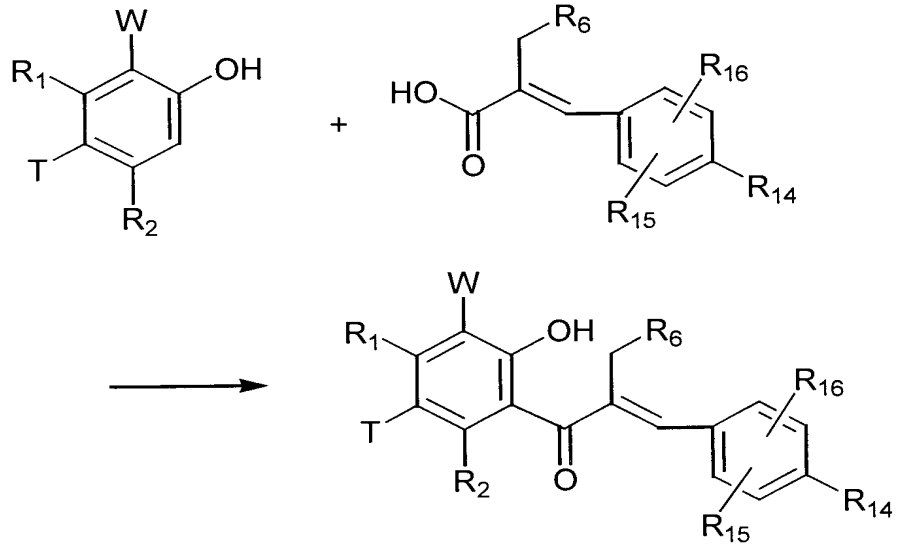

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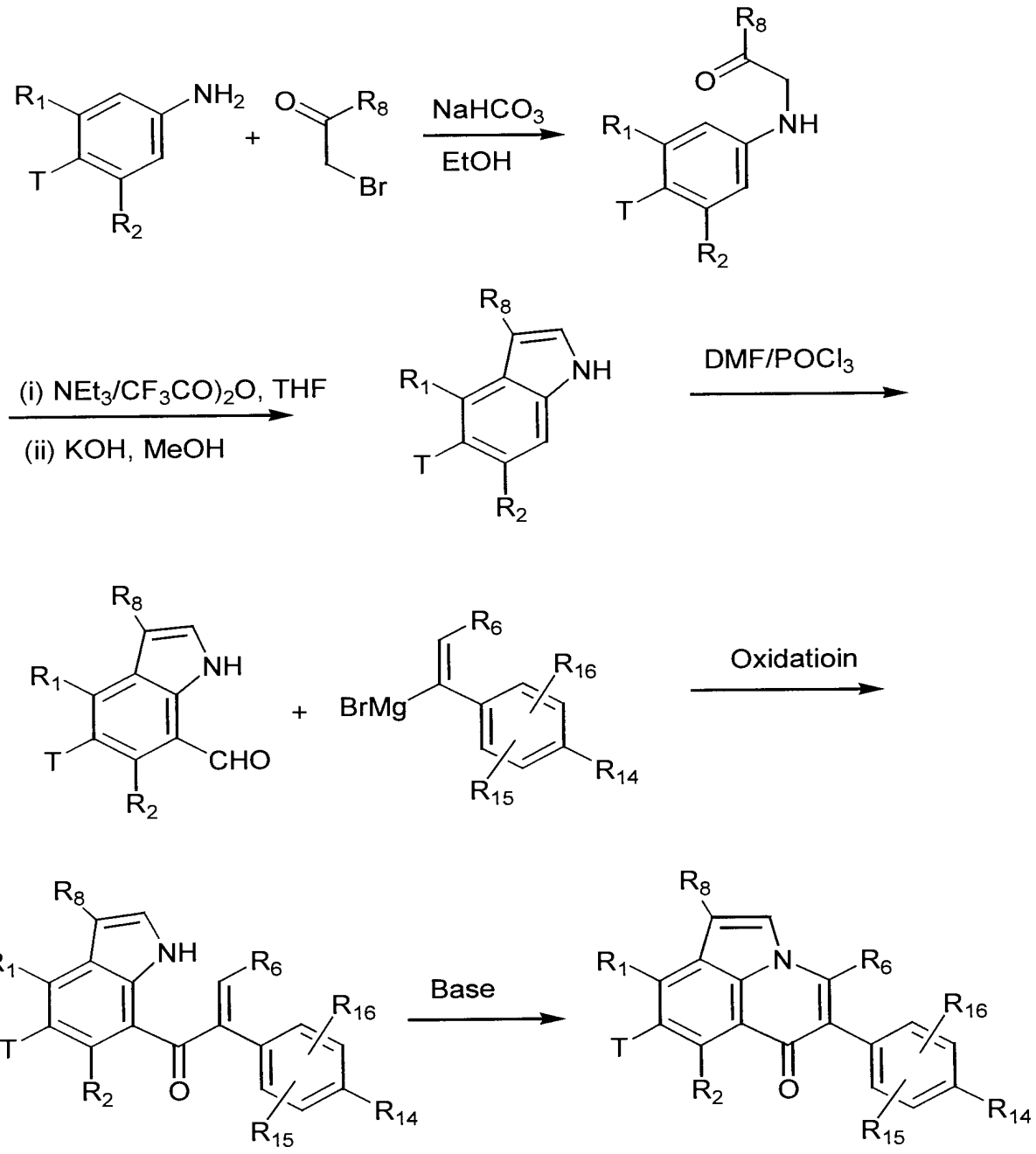
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T
R2
O
R8
Br
+
NaHCO3
EtOH
R8
O
NH
R1
T
R2
(i) NEt3/CF3CO)2O, THF
(ii) KOH, MeOH
R8
NH
R1
T
R2
DMF/POCl3
R8
NH
R1
T
CHO
R2
+
R6
BrMg
R16
R14
R15
Oxidatioin
R8
NH
R1
T
R2
R6
O
R16
R14
R15
Base
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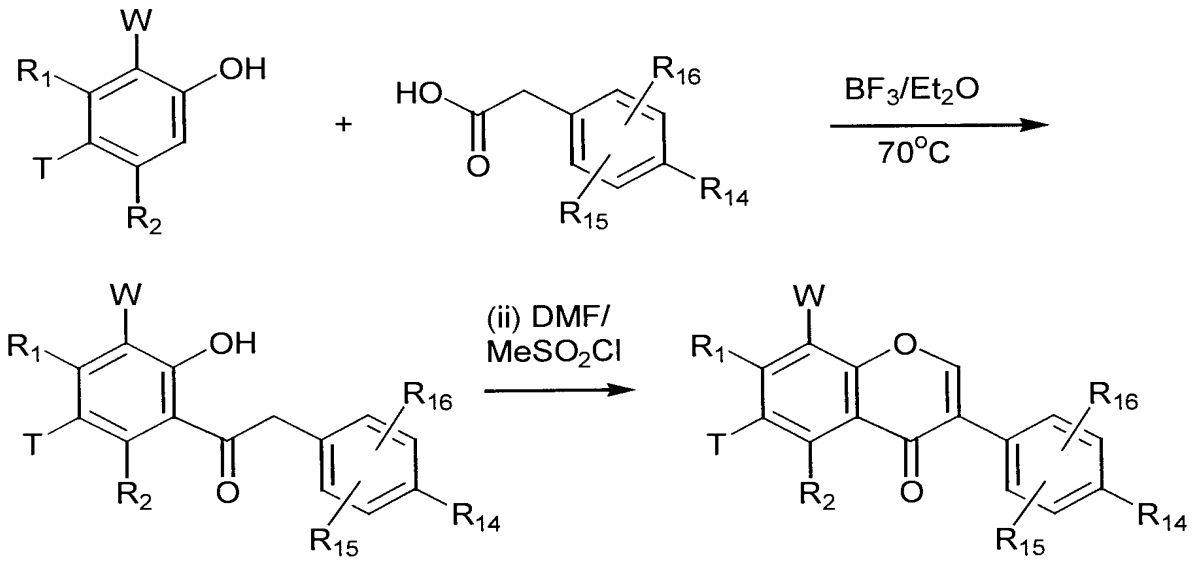
R2
R6
O
R16
R14
R15

Scheme 7



Scheme 8

EXAMPLE 1

General Syntheses of Substituted Isoflavones

6-Chloro-4',7-dihydroxyisoflavone was synthesised by the condensation of 4-chlororesorcinol with 4-hydroxyphenylacetic acid to afford 5-chloro-2,4,4'-trihydroxydeoxybenzoin. Cyclisation of the intermediate deoxybenzoin was achieved by treatment with dimethylformamide and methanesulfonyl chloride in the presence of boron triflouride etherate.

By varying the substitution pattern on the resorcinol or phenylacetic acid groups numerous other substituted isoflavones can also be synthesised in a similar manner. For example starting with 5-methyl resorcinol affords 4',7-dihydroxy-5-methylisoflavone, whilst use of 3-hydroxy phenyl acetic acid in the general synthetic method affords 3'-hydroxy isoflavone derivatives.

Isoflavan-4-ones

EXAMPLE 2

Synthesis of 6-Chloro-4',7-diacetoxyisoflavone

A mixture of 6-chloro-4',7-dihydroxyisoflavone (1.25 g, 4.3 mmol), acetic anhydride (7.5 ml) and pyridine (1.4 ml) was heated in an oil bath at 105-110° C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with aqueous methanol (50%) and dried to yield 6-chloro-4',7-diacetoxyisoflavone (1.2g, 75%) as colourless prisms. ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $OCOCH_3$), 2.41 (s, 3H, $OCOCH_3$), 7.16 (d, 2H, J 8.6 Hz, ArH), 7.36 (s, 1H, H8), 7.57 (d, 2H, J 8.6 Hz, ArH), 8.00 (s, 1H, H5), 8.37 (s, 1H, H2).

EXAMPLE 3

Synthesis of 6-Chloro-4',7-diacetoxyisoflavan-4-one

Adam's catalyst (0.045g) was added to a solution of 6-chloro-4',7-diacetoxyisoflavone (0.25g, 0.7 mmol) in ethyl acetate (30 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 6-chloro-4',7-diacetoxyisoflavan-4-one (0.15g, 60%) as colourless plates. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 2.37 (s, 3H, $OCOCH_3$), 3.98 (dd, 1H, J 6.0 Hz, 7.5 Hz, H3), 4.68 (m, 2H, H2), 6.87 (s, 1H, H8), 7.07 (d, 2H, J 8.6 Hz, ArH), 7.27 (d, 2H, J 8.6 Hz, ArH), 8.01 (s, 1H, H5).

EXAMPLE 4

Synthesis of 6-Chloro-4',7-dihydroxyisoflavan-4-one

Imidazole (0.60g) was added to a suspension of 6-chloro-4',7-diacetoxyisoflavan-4-one (0.24g, 0.06 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered, washed with water and dried to yield 6-chloro-4',7-

dihydroxyisoflavan-4-one (0.14g, 75%) as a white powder. 1H NMR (d_6-acetone): δ 3.87 (t, 1H, J 7.2 Hz, H3), 4.64 (d, 2H, J 6.2 Hz, H2), 6.59 (s, 1H, H8), 6.78 (d, 2H, J 8.7 Hz, ArH), 7.10 (d, 2H, J 8.7 Hz, ArH), 7.70 (bs, 1H, OH), 7.77 (s, 1H, H5).

EXAMPLE 5

Synthesis of 4',7-Diacetoxy-5-methylisoflavone

A mixture of 4',7-dihydroxy-5-methylisoflavone (1.51g, 5.6 mmol), acetic anhydride (9 ml) and pyridine (1.7 ml) was heated in an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from methanol to yield 4',7-diacetoxy-5-methylisoflavone as colourless prisms (1.8g, 91%). m.p. 195-97°C, ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $OCOCH_3$), 2.35 (s, 3H, $OCOCH_3$), 2.87 (s, 3H, Me), 6.92 (bs, 1H, H8), 7.12 (bs, 1H, H5), 7.16 (d, 2H, J 8.7 Hz, ArH), 7.55 (d, 2H, J 8.7 Hz, ArH), 7.89 (s, 1H, H2).

EXAMPLE 6

Synthesis of 4',7-Diacetoxy-5-methylisoflavan-4-one

Palladium on barium sulfate (5%, 0.06g) was added to a solution of 4',7-diacetoxy-5-methylisoflavone (0.30g, 0.8 mmol) in ethyl acetate (50 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 4',7-diacetoxy-5-methylisoflavan-4-one (0.20g, 67%) as colourless plates. m.p. 143-45°C, ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 2.30 (s, 3H, $OCOCH_3$), 2.62 (s, 3H, Me), 3.95 (t, 1H, J 7.2 Hz, H3), 4.62 (d, 2H, J 6.8 Hz, H2), 6.59 (d, 1H, J 2.2 Hz, H8), 6.66 (d, 1H, J 2.2 Hz, H5), 7.07 (d, 2H, J 8.3 Hz, ArH), 7.28 (d, 2H, J 8.3 Hz, ArH).

EXAMPLE 7

Synthesis of 4',7-Dihydroxy-5-methylisoflavanone

Imidazole (0.63g) was added to a suspension of 4',7-diacetoxy-5-methylisoflavan-4-one (0.50g, 1.4 mmol) in absolute ethanol (20.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered, washed with water and dried to yield 4',7-dihydroxy-5-methylisoflavan-4-one (0.25g, 66%) as a white powder. ^{1}H NMR (d_6-acetone): δ 2.51 (s, 3H, Me), 3.76 (t, 1H, J 5.7 Hz, H3), 4.57 (d, 2H, J 7.1 Hz, H2), 6.26 (d, 1H, J 2.2 Hz, H8), 6.35 (d, 1H, J 2.2 Hz, H5), 6.78 (d, 2H, J 8.7 Hz, ArH), 7.11 (d, 2H, J 8.7 Hz, ArH).

Isolflavan-4-ols and Isoflav-3-enes

EXAMPLE 8

Synthesis of 4'-7-Diacetoxy-5-methylisoflavan-4-ol

4'-7-Diacetoxy-5-methylisoflavan-4-ol was prepared by the reduction of 4'-7-diacetoxy-5-methylisoflavone (0.25g) with Adam's catalyst in ethyl acetate (30 ml) under a hydrogen atmosphere for 72 hours. The solution was filtered through a pad of Celite to yield predominantly *cis*-4'-7-diacetoxy-5-methylisoflavan-4-ol. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, $OCOCH_3$), 2.30 (s, 3H, $OCOCH_3$), 2.62 (s, 3H, Me), 3.24 (dt, 1H, J 3.4 Hz, J 11.8 Hz, H3), 4.31 (ddd, 1H, J 1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.57 (dd, 1H, J 10.5 Hz, 11.8 Hz, H2), 4.82 (bs, 1H, H4), 6.51 (d, 1H, J 2.1 Hz, H8), 6.59 (d, 1H, J 2.1 Hz, H6), 7.06 (d, 2H, J 8.6 Hz, ArH), 7.29 (d, 2H, J 8.6 Hz ArH).

EXAMPLE 9

Synthesis of 4',7-Diacetoxy-5-methylisoflav-3-ene

4',7-Diacetoxy-5-methylisoflav-3-ene was prepared by the dehydration of cis- and trans-4'-7-diacetoxy-5-methylisoflavan-4-ol (0.2g) with phosphorus pentoxide (2.0g) in dry dichloromethane (20 ml). The crude product was chromatographed on silica column using dichloromethane as the eluent. ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 2.31 (s, 3H,

$OCOCH_3$), 2.36 (s, 3H, Me), 5.08 (s, 2H, H2), 6.49 (d, 1H, J 2.0 Hz, H8), 6.52 (d, 1H, J 2.2 Hz, H5), 6.89 (s, 1H, H4), 7.14 (d, 2H, J 8.6 Hz, ArH), 7.44 (d, 2H, J 8.6 Hz, ArH).

EXAMPLE 10

Synthesis of 4',7-Dihydroxy-5-methylisoflav-3-ene

4',7-Dihydroxy-5-methylisoflav-3-ene was prepared from 4',7-diacetoxy-5-methylisoflav-3-ene by the removal of the acetoxy groups by hydrolysis under standard conditions.

EXAMPLE 11

Synthesis of 3',5,7-Trihydroxyisoflavylium chloride

Phosphoryl chloride (1.75 ml) was added to a mixture of the monoaldehyde (0,95g) and phloroglucinol dihydrate (1.6g) in acetonitrile (10 ml). The mixture was stirred at 30°C for 20 minutes and then at room temperature for 3 hours. The orange precipitate was filtered and washed with acetic acid to yield the isoflavylium salt.

EXAMPLE 12

Synthesis of Isoflav-3-ene-3',5,7-triol

Isoflav-3-ene-3',5,7-triol was prepared by the reduction of 3',5,7-trihydroxyisoflavylium chloride (0.5g) with sodium cyanoborohydride (0.33g) in ethyl acetate (11 ml) and acetic acid (3 ml) and chromatographic separation of the resulting mixture of isoflav-3-ene and isoflav-2-ene mixture. ^1H NMR (d_6-acetone): δ 4.99 (s, 2H, H2), 5.92 (d, 1H, J 2.0 Hz, ArH), 6.04 (d, 1H, J 2.2 Hz, ArH), 6.78-7.18 (m, 5H, ArH).

Isoflavans

EXAMPLE 13

Synthesis of Isoflavan-5,7-diol

Isoflavan-5,7-diol was prepared by the reduction of a suspension of 5,7-dihydroxyisoflavylium chloride (0.5g) with Palladium-on-charcoal (5%, 0.1g) in acetic acid (15 ml) containing ethyl acetate (2.5 ml) under a hydrogen atmosphere. The crude

product was recrystallised from 1,2-dichloromethane to give the isoflavan as colourless needles, m.p. 76-78°C (lit m.p. 77-79°C).

EXAMPLE 14

Synthesis of 4',5,7-Triacetoxyisoflavan

4',5,7-Triacetoxyisoflavan was prepared by the reduction of a suspension of 4',5,7-trihydroxyisoflavylium chloride (0.31g) with platinum oxide (0.04g) in a mixture of acetic anhydride (2.0 ml) and ethyl acetate (10 ml) under a hydrogen atmosphere. After the removal of catalyst the crude product was refluxed with pyridine (0.5 ml) and the resulting triacetate was isolated by evaporation of the solvent and crystallisation of the residue. M.p. 126-28°C.

EXAMPLE 15

Synthesis of Isoflavan-4',5,7-triol

Isoflavan-4',5,7-triol was prepared from 4',5,7-triacetoxyisoflavan by the removal of the acetyl groups by hydrolysis. M.p. 206-8°C.

EXAMPLE 16

The binding affinity of various compounds of the invention for both subtypes of the estrogen receptor was determined with the "Estrogen Receptor Alpha or Beta Competitor Assay Core HTS Kit" supplied by Panvera Corporation (Product No. P2614/2615). 6-Chloro-4',7-dihydroxyisoflavan-4-one showed good competitive binding to the estrogen receptor with the following results:

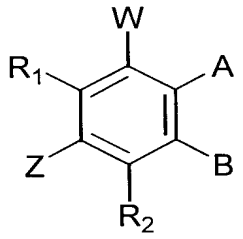
ER alpha receptor = 37.82 uM
ER beta receptor = 32.14 uM

The results show that the compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic effects, vasodilatory and spasmodic effects, inflammatory effects and oxidative effects.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The claims defining the invention are as follows:

1. An isoflavone compound or analogue thereof of the general formula I:



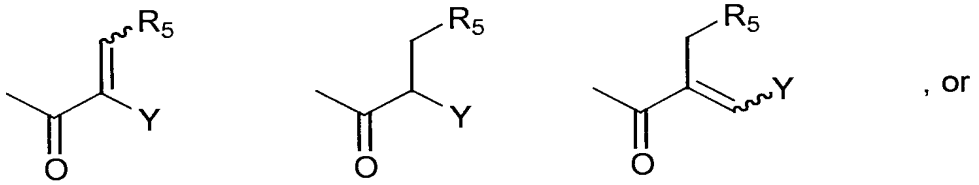
(I)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

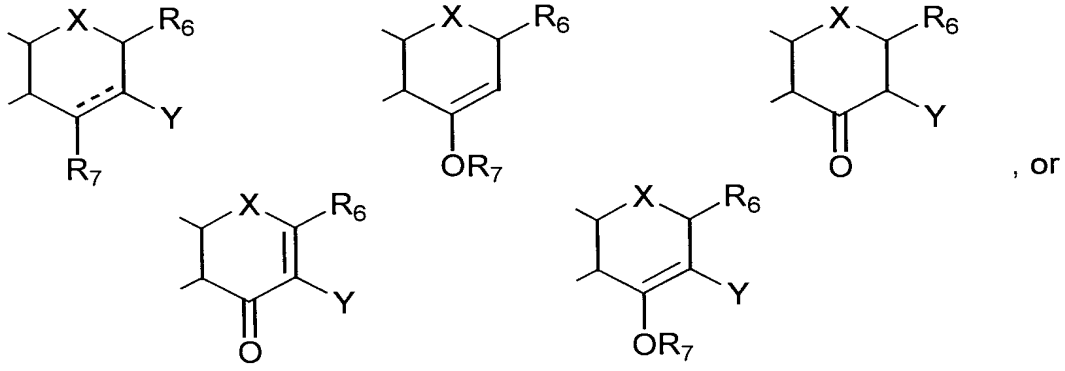
Z is hydrogen, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from



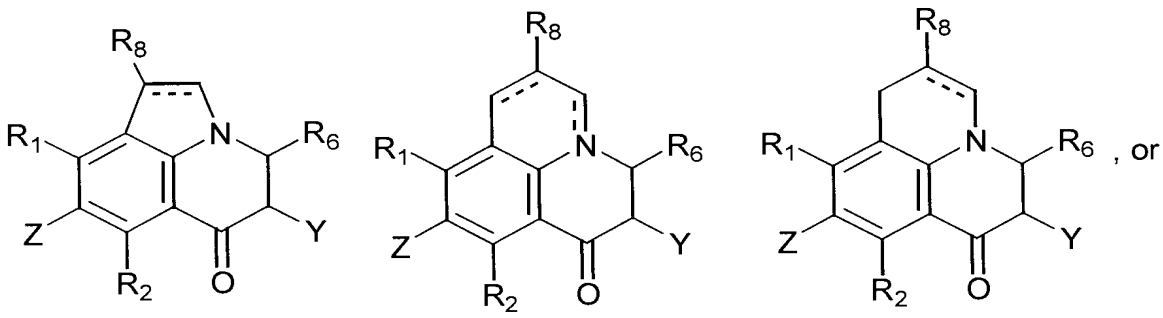
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from

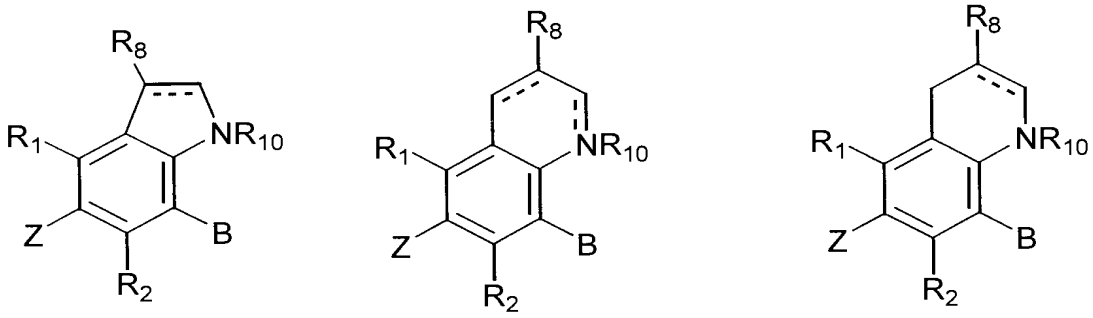


, or

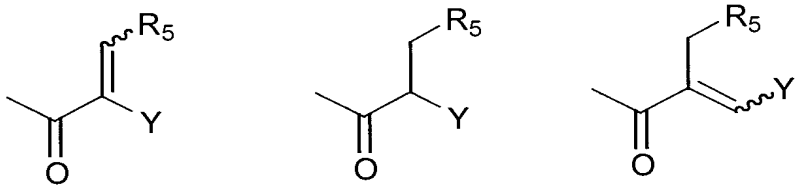
W, A and B taken together with the groups to which they are associated comprise



W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

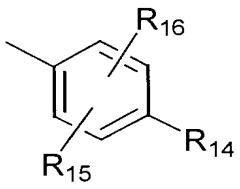
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

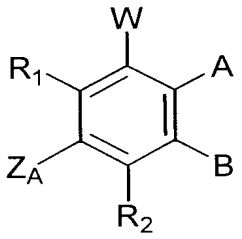
R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_1 is not hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid.

2. An isoflavone compound or analogue thereof of the general formula II:



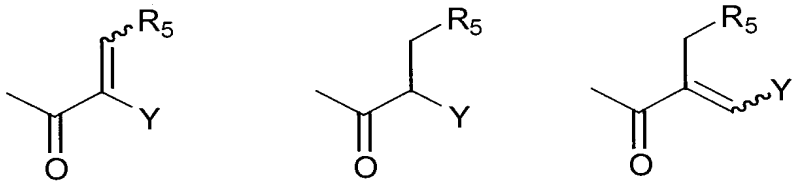
(II)

in which

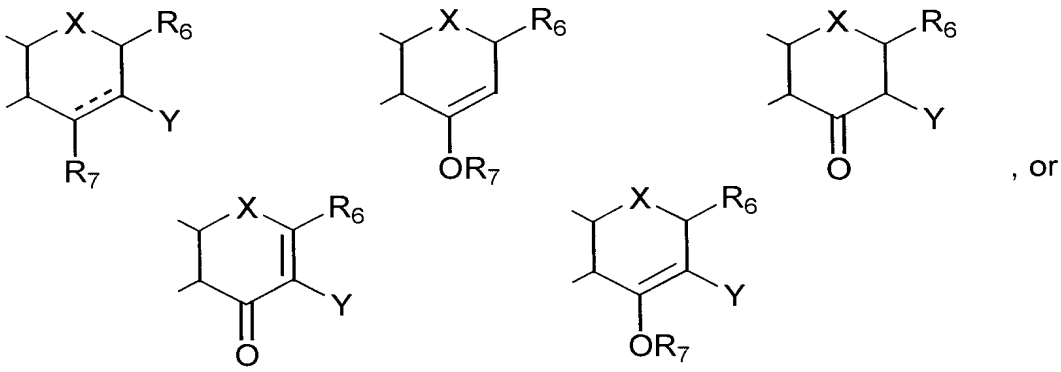
R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z_A is OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

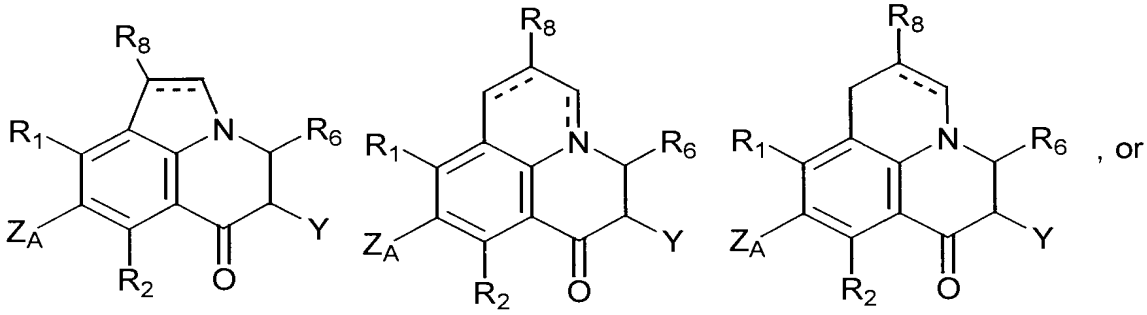
W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from


, or

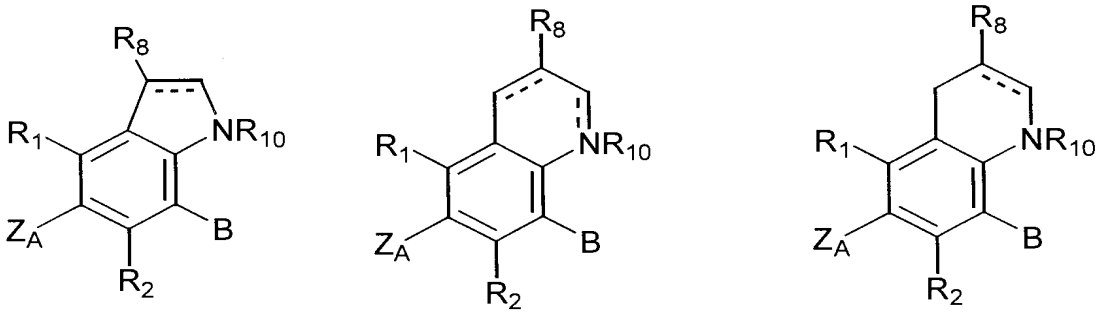
W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from


, or

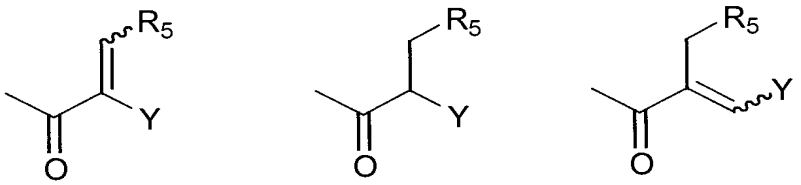
W, A and B taken together with the groups to which they are associated comprise


, or

W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

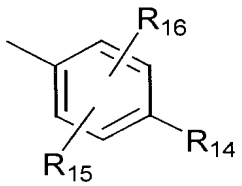
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

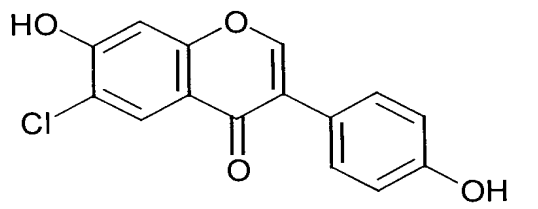
Y is

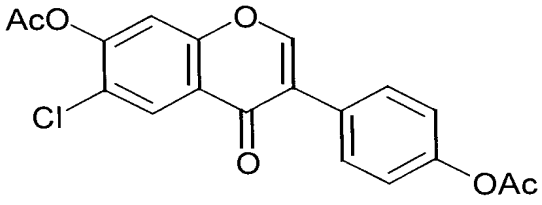


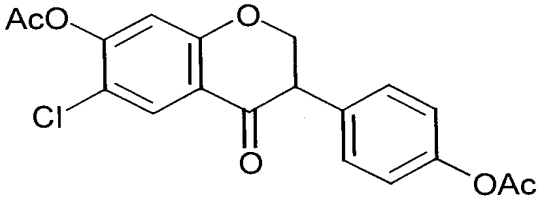
wherein

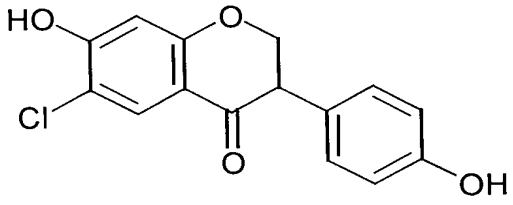
R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo.

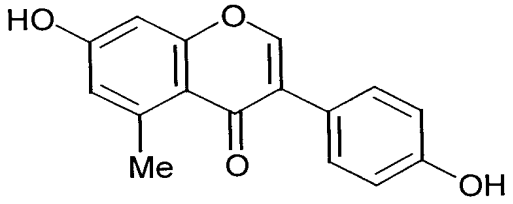
3. A compound of formulae I as defined in claim 1 or of formula II as defined in claim 2 selected from the group consisting of:

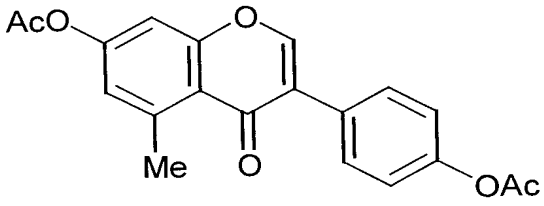


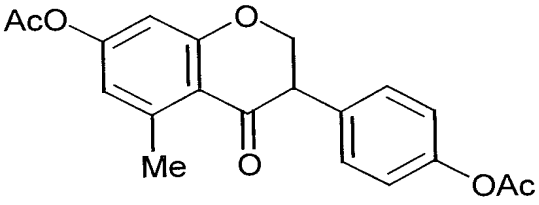


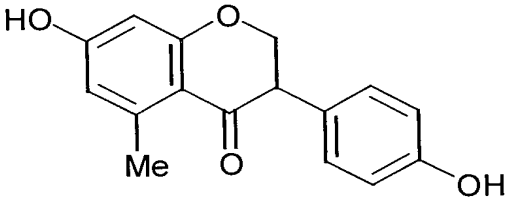


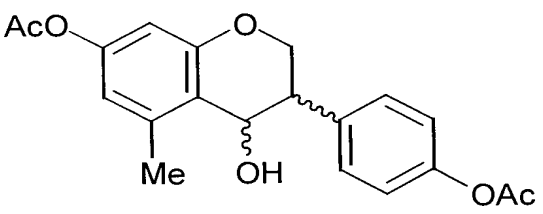


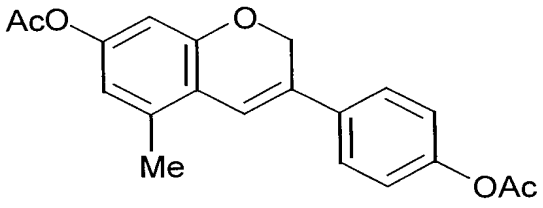


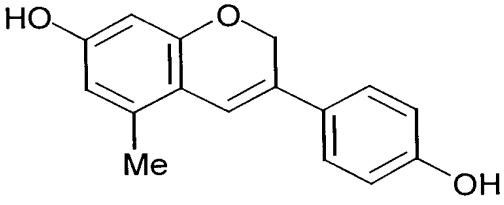


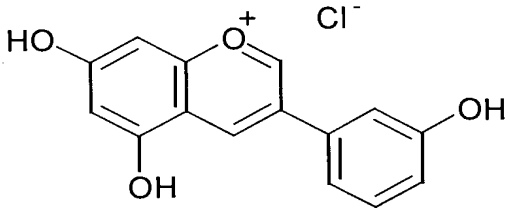


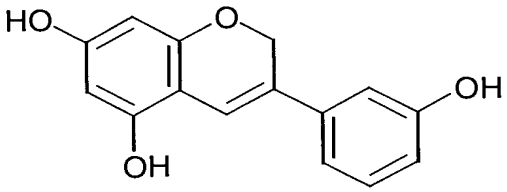


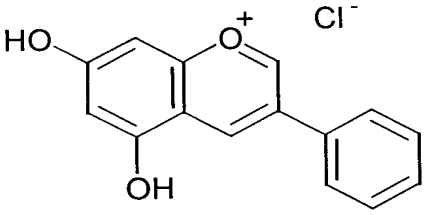

AcO
O
Me
OH
OAc

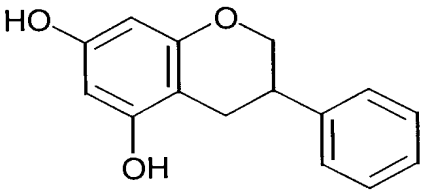

AcO
O
Me
OAc

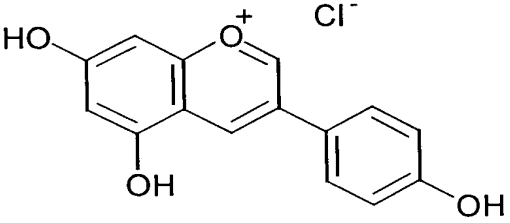

HO
O
Me
OH

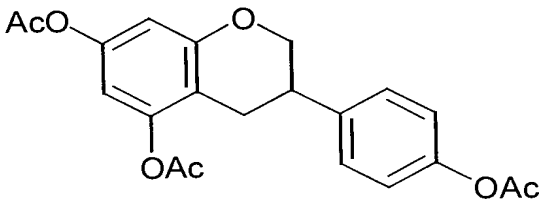

HO
O+
Cl-
OH
OH

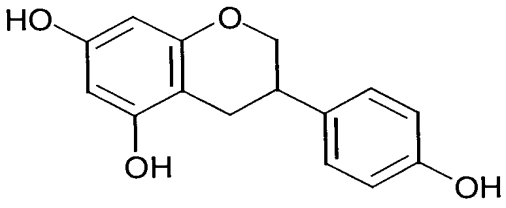

HO
O
OH
OH


HO
O+
Cl-
OH


HO
O
OH


HO
O+
Cl-
OH
OH


AcO
O
OAc
OAc


HO
O
OH
OH

4. A method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; artherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds selected from formulae I and II.

5. Use of one or more compounds selected from formulae I and II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more therapeutic indications according to claim 4.

6. Use of one or more compounds selected from formulae I and II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more therapeutic indications according to claim 4.

7. An agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications according to claim 4 which comprises one or more compounds selected from formulae I and II either alone or in association with one or more carriers or excipients.

8. A therapeutic composition which comprises one or more compounds selected from formulae I and II in association with one or more pharmaceutical carriers and/or excipients.

9. A drink or food-stuff, which contains one or more compounds selected from formulae I and II.

10. A microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds selected from formulae I and II.

11. One or more microorganisms which produce one or more compounds selected from formulae I and II.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/01056

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 311/36, 311/38, 471/06, C07C 49/215, 49/ 213, A61K 352, 31/12, 31/437, A61P 5/00, 25/22, 25/24, 9/10, 19/10, 19/02, 17/06, 7/00, 35/00, 25/28, 17/04, 1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN substructure search, Isoflavone backbone ;
CA chemical name search of examples.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Aust. J. Chem., Volume 31, No: 2, Issued 1978, Lamberton et al, "Catalytic hydrogenation of Isoflavones", pages 455-7. See in particular page 456 compounds 1, 4,8,9 and 10.	1, 3
X	Phytochemistry, vol 29 No 3, Issued 1990, Weidenborner et al, "Antifungal activity of isoflavonoids..." pages 801-3. See page 802 compounds B_1, B_2, B_3, D_3, G_3, H_3, I_3	1, 2
X	Aust. J. Chem., Volume 34, No 12, issued 1981, Liepa et al, "A synthesis of hydroxylated isoflavylium....", pages 2647-55. See page 2649 compounds 4a, 9a, 9b, 9d, 9f, 10a, 10b, 10c.	1, 3

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2000	27 NOV 2000
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer K. LEVER Telephone No : (02) 6283 2254

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/01056

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Electrochem. Soc. India, Volume 47, No. 4, issued 1998, Bannerjee et al, "Polarography of flavanone and isoflavanone", pages 237-244. See page 239.	1
X	Heterocycles, Volume 28, No.1, issued 1989, Wahala et al, "Hydrogen transfer reduction of Isoflavones", pages 183-186. See page 185.	1
X	WO 99/36050 A1 (NOVOGEN RESEARCH PTY. LTD.) publication date 22 July 1999. See formulas 1 and 2 on page 6 and compounds 17-19.	1
X	WO 99/18953 A1 (CHILDREN'S HOSPITAL OAKLAND RESEARCH INSTITUTE) publication date 22 April 1999. See document in general and compounds on page16 Table II.	1, 2
X	WO 98/08503 A1 (NOVOGEN RESEARCH PTY.LTD.) publication date 5 March 1998. See whole document.	1, 4-9
X	WO 98/48790 A1 (ANTICANCER INC.) publication date 5 November 1998. See whole document.	1,2,4-8
X	FR 2693724 A1 (LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) publication date 21 January 1994. See example 1 and 2.	1,2,3
X	Patent Abstracts of Japan, JP 1-226824 A (OTA ISAN: KK) publication date 11 September 1989. See abstract	1,2
X	US 4157984 (ZILLIKEN) publication date 12 June 1979. See formula I, column 4 line 30, column 2 lines 10-19 and the abstract.	2, 4-9
P,X	WO 00/03707 A1 (LABORATOIRE L. LAFON) publication date 27 January 2000, See examples	1
X	DE 4432947 A1 (NEW STANDARD GmbH) publication date 21 March 1996 See column 2	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/01056

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: I (Unsearchable Claims)

Claims 1, 2, 4-9 have not fully been searched for economical reasons. These claims are broad and largely unsupported by the description with no examples to the majority of compounds encompassed by the claims.

Claims 10 and 11 have not been searched because there is no support for any microorganisms in the description.

Claim 3 has been fully searched.

INTERNATIONAL SEARCH REPORT

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Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos: **1,2, 4-9 in part and claims 10 and 11 in full.**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See supplement sheet.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU00/01056

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	99/36050	AU	16518/99	EP	1049451		
WO	99/18953	AU	10939/99	EP	1024803	US	5972995
WO	98/08503	AU	40034/97	EP	954302	GB	2331015
WO	98/48790	AU	71657/98				
JP	01226824		NO	FAMILY	MEMBERS		
US	4157984	US	4234577	EP	25783	WO	8002027
		DE	2967100	JP	56500493		
WO	00/003707	AU	46282/99	FR	2781154		
FR	2693724		NO	FAMILY	MEMBERS		
DE	4432947		NO	FAMILY	MEMBERS		
							END OF ANNEX